further comprising the step of topical administration of a coagulant at the site of bleeding.

14. (twice amended) A composition for inhibition of microvascular bleeding comprising an inhibitor of a natural anticoagulant selected from the group consisting of protein C, thrombomodulin, antithrombin III, heparin cofactor II and tissue factor [inhibitor] pathway inhibitor in a pharmaceutically acceptable carrier for systemic administration to a patient in combination with a coagulant in a pharmaceutically acceptable carrier for topical administration to a patient.

Please add the following claims:

18. The method of claim 1 wherein the inhibitor is administered topically.

19. The method of claim 18 further comprising the step of topical administration of a coagulant at the site of bleeding.

Remarks

The present invention is a method for inhibiting microvascular bleeding at a site in a patient exhibiting microvascular bleeding which includes administering to the patient an effective amount of a compound in a pharmaceutical carrier to block greater than 90% of activated protein C in human plasma, where the compound is an inhibitor of either anticoagulant protein C, antithrombin III, heparin cofactor II, thrombomodulin, or tissue factor pathway inhibitor. The present invention also includes the aforementioned compound in a pharmaceutical carrier for systemic administration, in combination with a coagulant in a pharmaceutical carrier for topical administration.

New claims 18 and 19 specify that the inhibitor may be administered topically in combination with an anticoagulant.

Support for the new claims is found at page 14, lines 13-17 of the Specification.

35 U.S.C. § 101

Claims 1-9, and 11-16 remain rejected under 35 U.S.C. § 101 as inoperative and therefore lacking utility. This rejection is respectfully traversed.

Applicants have provided *in vivo* examples demonstrating efficacy

The Examples, using a porcine model, clearly demonstrate that the protein C inhibitors are not inactivated before having an effect, the protein does reach the target area, and there were no adverse side effects [Specification, p. 16, line 32 to p. 21, line 35]. Furthermore, Applicants note that the Specification at p. 14, lines 21-27, presents recommended dosages for human patients.

The animal models are predictive of efficacy in humans

Animal tests are adequate proof of utility under 35 U.S.C. § 101 where the art would accept those tests as appropriately correlated with human utility. In re Hartop, 311 F.2d 249 (C.C.P.A. 1962); In re Bergel, 292 F.2d 955 (C.C.P.A. 1961); M.P.E.P. § 608.01(p) (1992). It is well known that pigs are an excellent model for human skin, and that most burn and scarring studies are first done with pigs, then with humans. [*See* Bergel, at p. 957, "The holding of the Board of Appeals overlooks the widespread practice of carrying out pharmacological work in animals as a screening procedure...".] Applicants have enclosed several articles demonstrating that the pig is a standard model in the anticoagulant area for those of ordinary skill in this art. These articles are: B.J.W. Bowie, *et al.*, "Transplantation of normal bone marrow into a pig with severe von Willebrand's disease," Journal of Clinical Investigation, vol. 78, pp. 26-30, July 1986; J.H. Chesebro, *et al.*, "Anti-thrombotic therapy and

progression of coronary artery disease: anti-platelet versus anti-thrombins," Circulation, vol. 86, supplement III, pp. III-100 to III-111; D.N. Fass, *et al.*, "Factor VIII (Willebrand) antigen and ristocetin-Willebrand factor in pigs with von Willebrand's disease," Thrombosis Research, vol. VIII, pp. 319-327 (1976); V.D. Fuster, *et al.*, "Interaction of platelets with the endothelium in normal and von Willebrand pigs," pp. 187-196 in Thrombosis: Animal and Clinical Models, ed. H.J. Day, *et al.* (Plenum Press NY 1978); V. Fuster, *et al.*, "Spontaneous arterial lesions in normal pigs and pigs with von Willebrand's disease," pp. 315-317 in Atherosclerosis: Metabolic, Morphologic, and Clinical Aspects, Eds. G.W. Manning, *et al.* (Plenum Press NY 1977); T.R. Griggs, *et al.*, "Susceptibility to atherosclerosis in aortas and coronary arteries of swine with von Willebrand's disease," American Journal of Pathology, vol. 102, pp. 137-145 (1981); and W. Montagana, *et al.*, "The skin of the domestic pig," Journal of Investigative Dermatology, vol. 43, pp. 11-22 (1964). The Examiner is also directed to the examples on p. 16, line 32 to p. 21, line 35 of the Specification.

Murine antibodies are efficacious in treatment of humans

Applicants note that T.A. Waldmann, "Monoclonal antibodies in diagnosis and therapy," Science, vol. 252, pp. 1657-1662 (June 21, 1991), was published quite some time before the filing date of the present application. Applicants have enclosed a printout of a search of the Medline™ computerized database, using the terms "monoclonal antibody" and "therapy", which uncovered more than 1,000 publications during 1991 and 1992. Applicants submit that the broad June 1991 assertion of Mr. Waldmann simply has no applicability to the state of the technology in July 1992.

W.J. Harris, *et al.*, Tibtech., vol. 11, pp. 42-44 (1993), states that "there is wide-spread acceptance that there

is little future for the use of rodent mAbs for *in vivo* human therapy." However, Ortho Biotech, Inc. (Raritan, New Jersey) has sold the anti-CD III Murine MAb Orthoclone OKT™3 as an immunosuppressant since June 1986. Orthoclone OKT™3 is a murine MAb marketed as a human therapeutic agent and is neither chimeric nor a "humanized" MAb. Centoxin ™, approved by the FDA for clinical testing by Centocor for treatment of septicemia, is also a murine monoclonal antibody. It appears that Mr. Harris' comments may relate to marketing or economic issues rather than efficacy.

Anti-Protein C inhibitors are functional equivalents

Again submitted are copies of publications that demonstrate the equivalence of inhibition of protein S and protein C in facilitating coagulation: F. Taylor, *et al.*, "C4b-binding protein exacerbates the host response to *Escherichia coli*," Blood, vol. 78, pp. 357-363 (1991) and Journal of Trauma (Supplement), vol. 30, pp. 197-203 (1990), which demonstrate that inhibition of protein C by C4bp binding protein or by monoclonal anti protein S antibody resulted in microvascular thrombosis, infarction and hemorrhage of the kidney when combined with an inflammatory challenge of live *E. coli* (10% of the lethal dose). Neither the C4bp binding protein nor the sublethal *E. coli* alone caused microvascular coagulation, disseminated intravascular coagulation, or organ damage. Earlier work, F.B. Taylor, *et al.*, Journal of Clinical Investigation, vol. 79, pp. 918-925 (1987), demonstrated that inhibition of protein C activation generated a similar response in exactly the same model, when protein C activation was blocked with a monoclonal antibody to protein C, HPC-4. There is similar evidence with respect to the other claimed compounds, all of which are well characterized as to their ability to inhibit protein C. [*See, e.g.*, pp. 7-11 of the Specification].

35 U.S.C.§ 112, ¶ 1

Applicants thank the Examiner for his withdrawal of the rejection under 35 U.S.C. § 112, ¶1, of claims 1-9 and 11-16 set forth in paragraph 17, Section C, of the Office Action mailed March 1, 1993.

Claims 1-9 and 11-16 remain rejected, and the Specification objected to, under 35 U.S.C. § 112, ¶1, for failing to provide an enabling disclosure and failing to present a best mode of carrying out the invention. This rejection is respectfully traversed.

The Examiner has asserted, without evidence, that the claims are not enabled. Applicants reject this assertion, as explained below. Even if, for purposes of argument, the Examiner's assertion is given credence, as explained below, Applicants have submitted evidence more than sufficient to rebut the assertion. Therefore, the rejection should be withdrawn. In re Wands, 858 F.2d 731, 740 (Fed. Cir. 1988); Application of Dinh-Nguyen, 492 F.2d 856, 858 (C.C.P.A. 1974); Ex parte Obukowicz, 27 U.S.P.Q.2d (BNA) 1063 (B.O.P.A.I. 1993).

The application as filed discloses dosages for treating humans

Applicants again note that at p. 14, lines 21-27 of the Specification, they have provided recommended dosages for human patients. Obviously dosages will differ between individual patients, but determination of a proper dosage is a matter of routine experimentation by the attending physician.

The best mode is disclosed in the application as filed

The best mode is described on page 12, line 9-14, and page 14, lines 13-17, and 21-27, in both numerical terms and in functional terms, *i.e.*, in an amount sufficient to saturate all the circulating protein C molecules at the time of treatment in the amount equivalent to block greater than 90% of the potential

activated protein C activity in human plasma, or one milligram HPC-4 anti-protein C antibody/kilogram body weight.

Applicants again refer to the enclosed publications that demonstrate the equivalence of inhibition of protein S and protein C in facilitating coagulation, and note that there is similar evidence with respect to the other claimed compounds, all of which are well characterized as to their ability to inhibit protein C [*See* pp. 7-11 of the Specification]. As explained in the Specification:

> Other compounds that may be effective include compounds which inhibit protein S, thereby inhibiting activated protein C. Other agents include those which inhibit thrombomodulin, antithrombin III, heparin cofactor II, and tissue factor inhibitor pathway.

[Specification, page 12, line 31 to page 13, line 1].

Treatment can be prior to or subsequent to bleeding

The anti-protein C inhibitors all utilize the same mechanism to inactivate protein C: they form a complex which prevents interaction of protein C with the blood components required for clotting to occur. The mechanism of action of the anti-protein C antibody or other inhibitors is not dependent upon whether it is administered before or after the initiation of microvascular bleeding, since it can be present and interact with protein C prior to initiation of bleeding (as would be the preferred case in a surgical procedure such as removing a skin graft) or subsequent to, as in the case where injury occurs and is then treated.

A number of conditions having the same mechanism of action can be treated

Skin graft removal is but one of a number of complications which can be treated by the present invention.

Other conditions include burn wounds, or liver, splenic, or brain trauma where there is microvascular damage resulting in bleeding. [*See* Specification, p. 13, line 31 to p. 14, line 11]. Applicants decline to limit the claims in a manner denying themselves the protection to which they are entitled since all of these involve the same mechanism of action and mode of treatment.

35 U.S.C. § 112, ¶ 2

Claims 1-9 and 11-16 remain rejected under 35 U.S.C. § 112 ¶ 2, as being indefinite on the basis that "tissue factor inhibitor pathway" is unclear in claims 1 and 14, and that "in combination with topical administration of a coagulant at the site of bleeding" in claim 8 lacks antecedent basis in claim 1. These rejections are respectfully traversed, if applied to the amended claims.

Claims 1 and 14 have been amended to adopt the suggestion of the Examiner. Support for the amendments is found at p. 12, line 34 to p. 13, line 1. Claim 8 has been amended in accordance with the suggestion of the Examiner. Support for the amendment is found at p. 14, lines 13-15; p. 16, line 32 to p. 17, line 1; p. 18, lines 5-6.

35 U.S.C. § 102(e)

Applicants thank the Examiner for the withdrawal of the rejection of claims 1-4, 7, 10 and 15 under 35 U.S.C. § 102(e) over U.S. Patent No. 5,147,638 to Esmon, *et al.*

35 U.S.C. § 103

Applicants thank the Examiner for withdrawal of the rejection of claims 5, 6, 8, 9, 11-13, 14, 16, 17 under 35 U.S.C. § 103 over U.S. Patent No. 5,147,638 to Esmon, *et al.*, in view of Suzuki, *et al.*, "A Study on the Properties of Commercial Thrombin Preparations," Thrombosis Research, vol. 53, pp. 271-277, 1989.

Claims 1-4, 7, and 11-13 were newly rejected under 35 U.S.C. § 103 as obvious over U.S. Patent No. 5,202,253 to Esmon,

et al., in view of U.S. Patent No. 5,147,638 to Esmon, *et al.* Claims 5, 6, 8, 9, and 14 to 16 were rejected under 35 U.S.C. § 103 as obvious over U.S. Patent No. 5,202,253 to Esmon, *et al.*, in view of U.S. Patent No. 5,147,638 to Esmon, *et al.*, as applied to claims 1-4, 7, 11-13 above, and further in view of S. Suzuki, *et al.*, "A study on the properties of commercial thrombin preparations," Thrombosis Research, vol. 53, pp. 271-277 (1989). These rejections are respectfully traversed.

Applicants again note that the present invention is the discovery that an inhibitor of natural anticoagulants such as protein C can be used to stop microvascular bleeding in normal tissue. "Microvascular bleeding" means bleeding from the venules, capillaries, and arterioles. [Specification, at p. 13, lines 33-34].

The two patents to Esmon, *et al.*, disclose the treatment of tumors by the systemic administration of a compound blocking the protein C pathway. It is clear from the Esmon, *et al.*, patents that the administration of the protein C inhibitor does not have any observable effect on normal tissues, much less induce clotting of the microvasculature in normal tissues. Moreover, the tumors that are treated in the Esmon, *et al.*, patents are not characterized by bleeding of any sort at the time of treatment with anti-protein C and cytokine. This is directly opposite to the present situation where the treatment is to stop bleeding in normal tissue. There is no disclosure in the Esmon, *et al.*, patents of combining a topical treatment with a systemic treatment, since such a treatment would not be effective in killing tumors. Moreover, as noted above, even in the case of tumors, these are not characterized as bleeding, as in the present situation. Accordingly, one would not be able to extrapolate from one to the other.

The two Esmon patents have been described above. Suzuki, *et al.*, describes the use of topical thrombin to stop bleeding. However, there is nothing in Suzuki, *et al.*, that would lead one to combine a topical treatment with a systemic treatment to kill tumors utilizing an inhibitor of a naturally occurring anti-coagulant, in addition to the topical treatment.

Allowance of claims 1-9, 11-16, and 18-19, as amended, is earnestly solicited.

Respectfully requested,

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CERTIFICATE OF MAILING UNDER 37 C.F.R. §1.8(a)

I hereby certify that this paper, along with any paper referred to as being attached or enclosed, is being deposited with the United States Postal Service on the date shown below with sufficient postage as first-class mail in an envelope addressed to the Commissioner of Patents and Trademarks, Washington, D.C. 20231.

Date: April 29, 1994

Patricia Hilger